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Clinical investigations of the influence of various naloxone* doses on the newborn

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Maternally administered opiate analgesics may cause a respiratory depression of the newborn. Such respiratory depression is often not diagnosed with purely clinical methods such as the APGAR score. However, laboratory and clinical – experimental methods may demonstrate a neonatal depression more clearly [2, 3, 13].

It has been well documented that the maximal effect of meperidine occurs within 30–60 minutes after administration to the mother but that a neonatal depression may be recognized as late as 2–4 hours after administration of meperidine [2, 9, 12].

Opiate antagonists have frequently been recommended for the prophylaxis of postpartum adaption disturbances caused by opiates. Basically two kinds of antagonists exist [9]: Agonist-antagonists such as nalorphine and levallorphan on the one hand and pure antagonists such as naloxone on the other hand. Agonist-antagonists may cause a respiratory depression if they are over-dosed or if there is no opiate present on the receptor site. This effect is not present with naloxone. If naloxone is given to the mother 5–15 minutes before birth or is injected immediately postpartum into the umbilical vein, the agent will prevent a postpartum neonatal respiratory depression [4, 5, 6, 7, 8, 9, 10, 14]. Various doses have been recommended for the umbilical vein injection [4, 6, 7, 8, 9, 11].

The purpose of this study was to investigate the influence of various naloxone doses on the postpartum course of neonatal blood gases and acid-base status following injection into the umbilical vein.

1 Experimental design and experimental groups

The study was carried out in two parts. Part I refers to 40 newborns randomly distributed into four groups. The newborns of Group I/1 were the controls; they had the usual postpartum care and did not receive naloxone. Neonates in Group I/2 received 0.02 mg/kg naloxone into the umbilical vein, infants in Group I/3 received 0.03 mg/kg and those in Group I/4 0.04 mg/kg of naloxone.

In Part II there were 30 newborns randomly distributed into three groups. The infants in Group II/1 received immediately postpartum an umbilical venous injection of placebo, those in Group II/2 0.04 mg/kg naloxone, and those in Group II/3 0.04 mg naloxone.

Part II of this study was designed as a double blind study where examiner and follow-up examiner were not informed about the agent or the dose. Placebo and the varying amounts of naloxone doses were distributed in equal amounts of volume and thus indistinguishable. The mothers of all newborns received at a cervical dilation of 3–4 cm

* Narcan®, Endo-Lab, Inc.

0.1 mg/kg of dehydrobenzperidol and 0.4 mg/kg of meperidine intravenously. The usual clinical variables and blood gases were recorded 30 minutes after the administration. When labor pain increased again, another dose of 0.4 mg/kg of meperidine was injected intravenously at the mother's request. One, five and ten minutes after birth the Apgar status of the newborn, blood gas and acid-base examinations were performed. Blood gas and acid-base status was repeated at 30, 60 and 120 minutes after birth. The blood samples were obtained from the hyperemized heel. pH, PCO_2, base-excess standard bicarbonate, and PO_2 were obtained with the ASTRUP apparatus and the SIGGAARD-ANDERSON nomogram.

2 Results

2.1 Part I

The maternal age was between 25.5 and 28.2 years, their mean weight was 67.7 to 71.3 kg. The duration of labor was between 107.8 and 144.8 minutes, and the time between the last meperidine dose and birth was between 66 and 96.1 minutes. The intravenous dose of meperidine was 0.42 to 0.53 mg/minute, which corresponds to 0.39 to 0.44 mg/kg/hour.

The birth weight of the newborns in Part I of this study was between 3.255 and 3.550 kg.

At the time of delivery the mean maternal pH values were between 7.38 and 7.40, PCO_2 between 29.02 and 34.68, PO_2 between 85.5 and 90.4 mm Hg. The mean base-excess values were −5.76 to −6.17 mval/l.

There were no statistically relevant differences between the neonatal pH values in all four groups (Fig. 1). **The same was true for the neonatal PCO_2 values (Fig. 2).**

However, a statistically significant difference was seen for the difference of the PCO_2 values from the base line value at one minute (ΔPCO_2) 30 and 60 minutes after birth in groups 2 and 4 (0.02 and 0.04 mg/kg). **In the two naloxone groups the PCO_2 values decreased more markedly when compared to the control group at 30 and 60 minutes after birth (Fig. 3).**

Neither the absolute nor the difference values to the base line for PO_2 (ΔPO_2) were significantly different between the control group and the naloxone groups (Fig. 4).

Thus, it was documented that under the conditions of the experiment (dose of meperidine, interval between meperidine and birth, etc) there were no significant differences between the controls and

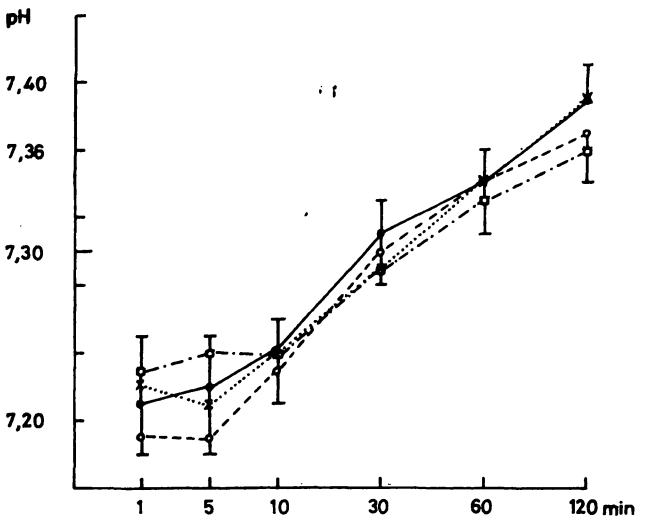

Fig. 1. pH values after birth in relation to various naloxone doses.
●——● controls
o——o 0.02 mg/kg naloxone
x . . . .x 0.03 mg/kg naloxone
■—.—.□ 0.04 mg/kg naloxone

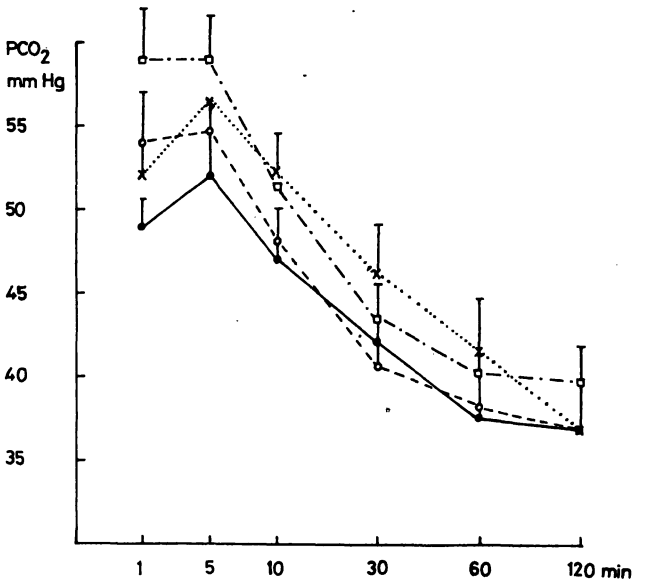

Fig. 2. PCO_2 values in neonates following various naloxone doses. See legend for Figure 1.

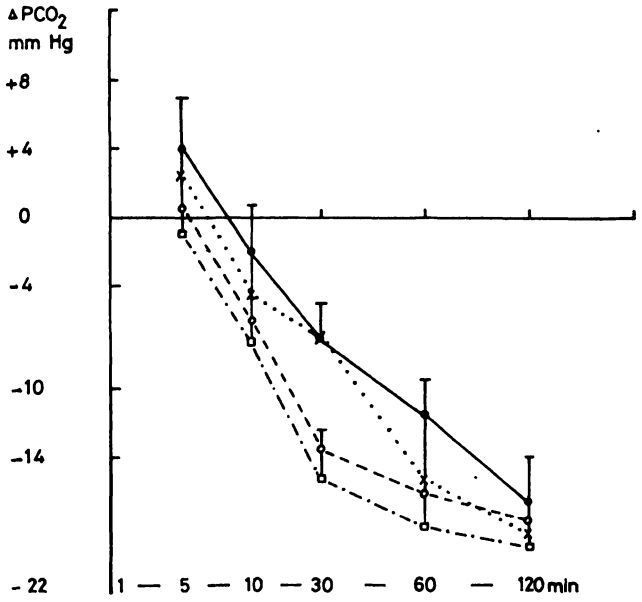

Fig. 3. Δ PCO_2 (= difference between PCO_2 at a particular point in time and the base line value 1 minute after birth). An increase of Δ PCO_2 indicates an increase of the PCO_2 value from the base line. See legends for Figure 1.

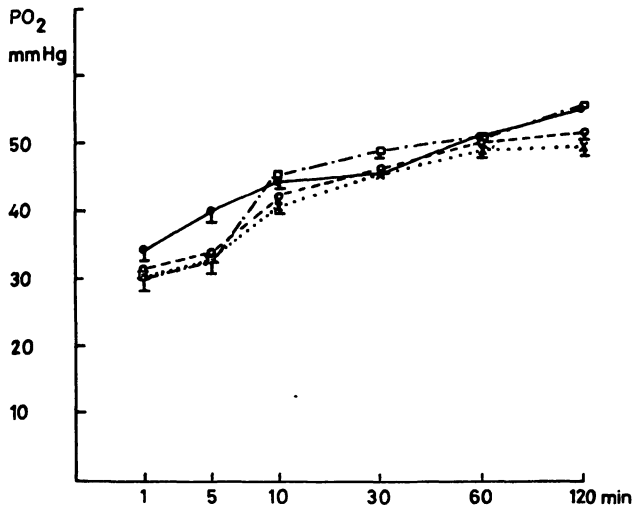

Fig. 4. PO_2 values in neonates in relation to various naloxone doses.

experimental groups: however, the decrease in the PCO_2 values in naloxone groups I/2 and I/4 were more marked than that in the control group. In order to verify this effect in a double blind experiment a new control group and a naloxone group with a dose of 0.04 mg/kg were compared with each other. Added to this experimental group were ten newborns who received only 0.04 mg of naloxone.

2.2 Part II

The age of the mothers in Part II was between 25.7 and 26.6 years, they weighed between 70.1 and 75.6 kg. Dehydrobenzperidol was given in total doses between 7.0 and 7.6 mg; the todal dose of meperidine was between 32.4 and 61.5 mg. The duration of labor was between 81.7 and 186.7 minutes, the administration of meperidine between 0.39 and 0.7 mg/minute or 0.33 to 0.56 mg/kg/hour respectively. The time between the last dose of meperidine and birth was 54.5 to 69.7 minutes. The newborns in Part II of the study weighed between 3247 and 3338 grams. Maternal pH, PCO_2, PO_2 and base-excess values in all three study groups of Part II were nearly identical and there were no statistically significant differences.

The pH values of the newborn were not statistically different in all three groups (Fig. 5). The same was true for the absolute PCO_2 values (Fig. 6). While the PCO_2 differences in comparison to the base line value were higher in both naloxone groups than the control group, this was statistically significant only for ten minutes after birth ($P < 0.05$); the differences were not significant for the other intervals (Fig. 7). **PO_2 and base-excess values did not differ in either the absolute values or the differences to the base line (Fig. 8).**

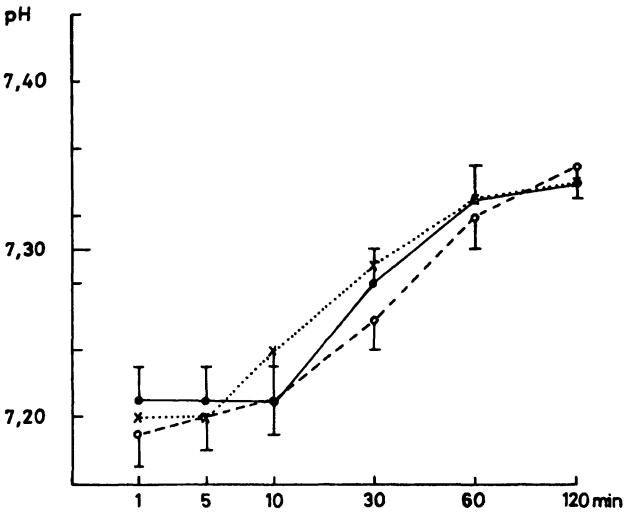

Fig. 5. PO_2 values in groups II/1–3
●——● controls
o– – –o 0.04 mg/kg naloxone
x. . . . x 0.04 mg naloxone
Indicated are means and standard deviation of the mean.

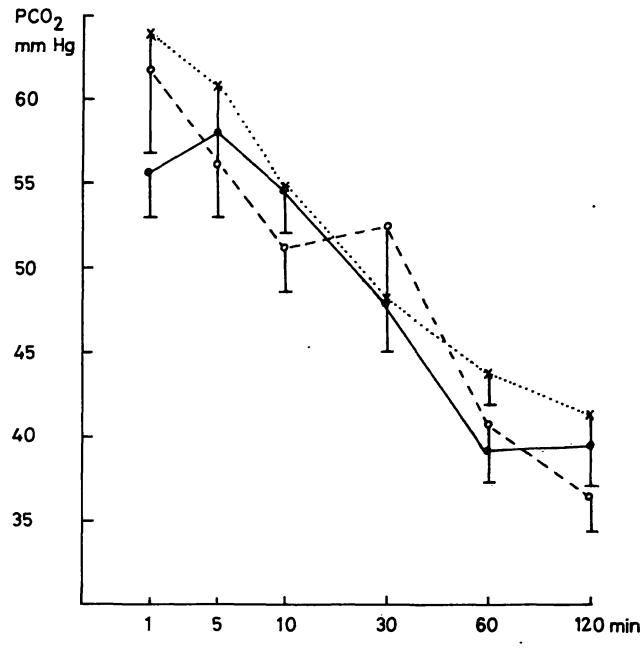

Fig. 6. PCO_2 values in groups II/1–3. See legend for Figure 5.

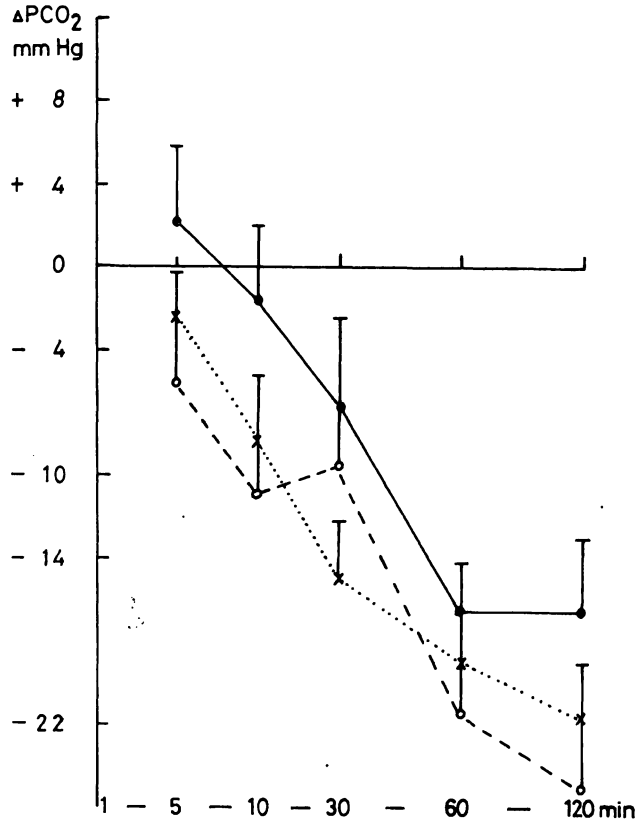

Fig. 7. Course of Δ PCO_2 in groups II/1–3. See legend for Figure 5.

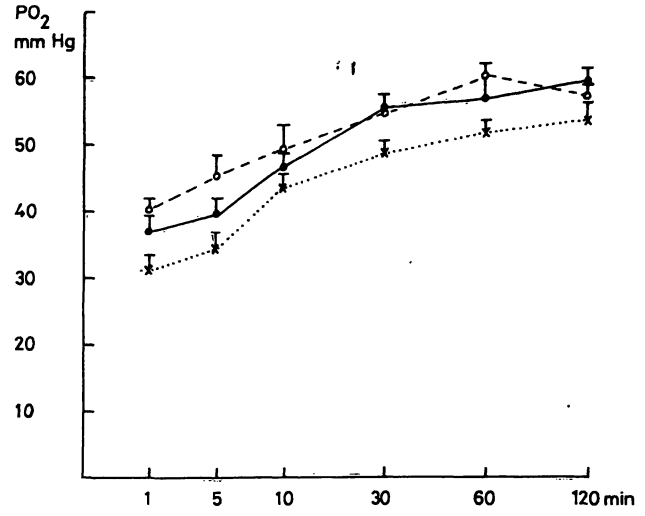

Fig. 8. Course of PO_2 values in groups II/1–3. See legend for Figure 5.

3 Discussion

The efficacy of intravenously administered naloxone for the prophylaxis and therapy of opiate-related neonatal respiratory depression has been demonstrated by various authors with different methods. GERHARDT et al [10] demonstrated an increase in ventilation following 0.1 mg/kg of narcan. The investigation of EVANS [7, 8] with 40 μg did not show any significant increase in respiratory frequency and alveolar ventilation but the PCO_2 values were markedly lower in the naloxone group than in the control group. Similar results were found by WIENDER and ROSEN [14].

In Part I of this study we demonstrated a markedly lower PCO_2 30 and 60 minutes after birth in the two groups (Δ PCO_2). The double blind study did not verify this effect at the same times, but there was a statistically significant difference five minutes after the administration of naloxone.

There is no difference in the postpartum PO_2 values between the various groups.

Thus, our results differ from the results of some authors but concur with the findings of CHANG et al, CLARK et al and MARTIN et al [4, 5, 11]. The reason for the different results has to be the dose of the agent and the different dose of meperidine. MARTIN [11] used mean meperidine doses of 97.4 mg, but did not record the total dose nor the

interval between the last dose and delivery. The study by CLARK [5] mentioned total doses of Meperidin between 150 and 500 mg distributed over several sub-doses. ROSEN and EVANS [7, 8, 14] record the total dose of meperidine administered and its level in the umbilical vein at the time of delivery but these authors did not measure capillary blood gas values and acidbase status while recording alveolar PCO_2 and CO_2 production.

The meperidine doses in our study are relatively low. According to the „Reisensburg recommendations" [1] intravenous application of low doses of meperidine establishes a base line sedation and analgesia; the patients at their request received additional low doses of analgesics intravenously.

Thus, the results of these various investigations differ in methodology and the dose of meperidine. Therefore, the basic situation of the experiment, namely, the degree of the postpartum respiratory depression of the newborn, differ in those studies. The primary reason for the differences should be the variously high doses of meperidine and the varying long intervals between last dose of meperidine and delivery. Possibly the routes of administration-intramuscularly vs intravenously-are also important.

Thus, it may be assumed in those studies in which a marked and statistically significant respiratory effect was demonstrated, that there was a notable respiratory depression of the newborn. In the group responding poorly only a minor degree of respiratory depression of the newborn may have been present. Thus, those newborns in which there was no effect should be classified as being depressed not due to opiates.

They demonstrate that naloxone in itself does not cause respiratory depression even if the agent is overdosed or there is no meperidine on the receptor site.

In summary, our study and those previously published allow the following conclusions:

1. **The use of naloxone in the newborn in the postpartum period has no negative effects** (in contrast to nalorphin and levallorphan)
2. **In the presence of respiratory depression there is a significantly faster CO_2 elimination** (higher ΔPCO_2 values) than without the use of naloxone.
3. **An optimal dose has not been established in this study.** While 0.04 mg/kg had a stronger effect in the first part of the experiment than 0.02 mg and 0.03 mg/kg, but it was also seen that 0.02 mg/kg was more effective than 0.03 mg/kg.

The second part of the study demonstrated that the administration of 0.04 mg/kg is as much or as little effective as is the injection of 0.04 mg as a total dose.

For clinical purposes the conclusion may be drawn that if an opiate-related respiratory depression of the newborn is suspected it may be treated without risk and with a dependable effect by the administration of naloxone.

Summary

The influence of postpartum injections of various doses of naloxone on the blood gases and acid base status of 70 newborns was investigated. In Part I of the experiment groups of 10 newborns each received 0.02, 0.03, or 0.04 mg/kg naloxone through the umbilical vein immediately after birth; there was a control group of 10 neonates. Part II of the experiment comprised three groups of ten newborns each received immediately after birth into their umbilical veins an injection of placebo (group 1), 0.04 mg/kg naloxone (group 2), or 0.04 mg naloxone (group 3). The second experiment was conducted as a double blind study.

All mothers received during labor 0.1 mg/kg dehydrobenzperidol and 0.4 mg/kg meperidine intravenously when the cervical dilatation was 3–4 cm. Additionally, 0.4 mg/kg of meperidine was given again if labor pain increased.

The mean duration of labor was between 81.7 and 186.7 minutes; the time between the last dose of meperidine and birth was between 54.4 and 96 minutes. The mean dose of meperidine was between 0.39 and 0.7 mg/minute or 0.33 to 0.56 mg/kg hour respectively. The course of the neonatal pH values PCO_2 and PO_2 up to two hours after birth in the first part of the experiment was not different. However, the ΔPCO_2, i.e. the difference of the PCO_2 values at the various measuring intervals from the base line value 1 minute after birth for groups 2 and 4 was statistically significantly lower at 30 and 60 minutes than the control group or group 3.

The experimental design of a double blind study in Part II of these studies again showed no differences in regard to pH, PCO_2, PO_2, or base-excess values. While the PCO_2 differences from the base line value were larger than the control group, this was significant only for ten minutes after birth.

Thus, the experiments allow the conclusion that **the use of naloxone in the neonate during the postpartum period has no negative effects. In respiratory depression the CO_2**

may be eliminated markedly faster than without the use of naloxone. Adequate doses are 0.04 mg as total dose or 0.01 or 0.02 mg/kg. An opiate-related respiratory depression of the newborn can be treated without risk and reliably by the use naloxone as an antagonist.

Keywords: acid-base status, analgesia, antagonist, birth, blood gases, dehydrobenzperidol, naloxone, neonate, meperidine, respiratory depression.

Zusammenfassung:

Klinische Untersuchungen zum Einfluß unterschiedlicher Naloxon-Dosen auf das Neugeborene post partum.
An insgesamt 70 Neugeborenen wurde der Einfluß der postpartalen Injektion unterschiedlicher Dosen von Naloxon auf die Blutgase und die Parameter des Säuren-Basen-Haushaltes untersucht. In Teil I erhielten je 10 Neugeborene 0,02 bzw. 0,03 bzw. 0,04 mg/kg Naloxon unmittelbar postpartal in die Nabelvene injiziert, 10 Neugeborene dienten als Kontrollgruppe. Teil II der Untersuchungen bezog sich auf 30 Neugeborene, die wiederum randomisiert auf 3 Gruppen verteilt waren. Die Neugeborenen der Gruppe 1 erhielten unmittelbar postpartal Placebo in die Nabelvene injiziert, die Neugeborenen der Gruppe 2 0,04 mg/kg Naloxon und die Neugeborenen der Gruppe 3 0,04 mg Naloxon. Teil II der Untersuchungen war als Doppelblindversuch angelegt.
Alle Mütter hatten unter der Geburt initial bei einer Muttermundsweite von 3–4 cm 0,1 mg/kg Dehydrobenzperidol und 0,4 mg/kg Dolantin intravenös injiziert erhalten. Sobald die Wehenschmerzen wieder zunahmen, wurden jeweils weitere 0,4 mg/kg Dolantin intravenös nachinjiziert.
Die Geburtsdauer betrug durchschnittlich zwischen 81,7 und 186,7 min, die Zeit zwischen der letzten Dolantin-Applikation und der Geburt zwischen 54,4 und 96 min. Der intravenöse Dolantin-Verbrauch lag im Mittel zwischen 0,39 und 0,7 mg/min bzw. 0,33–0,56 mg/kg/h.
Der bis zu 2 h nach der Geburt verfolgte neonatale pH-Wertverlauf ließ innerhalb des I. Teils der Untersuchungen keinen statistisch relevanten Unterschied erkennen. Das gleiche traf auf die PCO_2-Werte und die PO_2-Werte zu. Wurde jedoch Δ PCO_2 – d. h. die Differenz der PCO_2-Werte zu den jeweiligen Meßzeitpunkten gegenüber dem Ausgangswert 1 min nach der Geburt – gebildet, so ergab sich in den Gruppen 2 und 4 (0,02–0,04 mg/kg) ein statistisch signifikanter Unterschied gegenüber der Kontrollgruppe und der Gruppe 3; die PCO_2-Werte dieser beiden Gruppen waren 30 und 60 min nach der Geburt ausgeprägter abgefallen als die PCO_2-Werte der übrigen Gruppen.
Auch unter den Bedingungen des Doppelblindversuches – Teil II der Untersuchungen – zeigten sich im pH-Wertverlauf, im Verlauf der PCO_2-, PO_2- und Base-Excess-Werte keine statistisch relevanten Unterschiede zwischen den Gruppen. Wenn auch die PCO_2-Differenzen wiederum gegenüber dem Ausgangswert in beiden Naxolon-Gruppen erheblich größer waren als in der Kontrollgruppe, so ließ sich doch ein statistisch relevanter Unterschied lediglich 10 min nach der Geburt auf dem 5%-Niveau nachweisen (Δ PCO_2).
Damit lassen die durchgeführten Untersuchungen die Schlußfolgerung zu, daß die Applikation von Naloxon an das Neugeborene in der postpartalen Phase ohne negative Auswirkungen ist, daß in Anwesenheit einer Atemdepression eine deutlich schnellere CO_2-Elimination zu erwarten ist als ohne die Applikation von Naloxon und daß eine adäquate Dosierung bereits mit 0,04 mg als Gesamtdosis bzw. ca. 0,01–0,02 mg/kg erreicht wird. Wenn eine opiatbedingte respiratorische Depression des Neugeborenen vorliegt oder vermutet werden kann, läßt sich diese ohne Risiko und mit zuverlässigem Effekt durch Naloxon antagonisieren.

Schlüsselwörter: Antagonisten, Atemdepression, Blutgase, Dehydrobenzperidol, Geburt, Naloxon, Neugeborenes, Pethidin, Säure-Basen-Status, Schmerzbekämpfung.

Résumé:

Etude clinique sur l'influence de doses diverses de naloxone post partum chez les nouveaux-nés
Une étude a été faite chez 70 nouveaux-nés choisis au hasard sur l'influence de l'injection postpartale de doses diverses de naloxone sur les gaz sanguins et des paramètres de teneur acidobasique. L'analyse a porté en Ière partie sur 4 groupes de 10 nouveaux-nés, les trois premiers ayant reçu respectivement une injection postpartale immédiate dans la veine ombilicale de 0,02, 0,03 et 0,04 mg/kg de naloxone et le quatrième servant de groupe de contrôle. La IIème partie des analyses a porté, à titre de test témoin double sur 30 nouveaux-nés répartis en trois groupes. Ceux du groupe I ont reçu de la même façon une injection de placebo, ceux du groupe II 0,04 mg/kg de naloxone et ceux du groupe III 0,04 mg de naloxone.
Une injection intraveineuse de 0,1 mg/kg de déhydrobenzpéridol et de 0,4 mg/kg de dolantine avait été initialement administrée à toutes les mères lorsque l'ouverture de l'utérus avait atteint 3–4 cm; cette injection avait été suivie d'une ou de plusieurs autres de 0,4 mg/kg de dolantine à la reprise des douleurs.
Les accouchements ont duré en moyenne de 81,7 à 186,7 min., le temps écoulé entre la dernière administration de dolantine et l'accouchement se situant entre 54,4 et 96 min. La quantité totale moyenne de dolantine injectée a été de 0,39 à 0,7 mg/min. ou de 0,33 à 0,56 mg/kg/h.

En ce qui concerne la première partie des analyses, l'observation des valeurs de pH néonatal ainsi que du PCO_2 et du PO_2 durant les deux heures successives à l'accouchement n'a donné aucun résultat significatif. Par contre, Δ PCO_2 – c.àd. l'analyse des différences entre les valeurs de PCO_2 5, 10, 30, 60 et 120 min. après l'accouchement et les valeurs initiales du PCO_2 1 min. après l'accouchement – a montré un écart statistiquement important entre les groupes 2 et 4 d'une part et le groupe de contrôle d'autre part: l'administration de 0,02 et de 0,04 mg/kg de naloxone a provoqué, en effet, 30 et 60 min. après l'accouchement une baisse plus rapide et plus forte du PCO_2.

De même, dans le test témoin double – IIème partie des analyses – on n'a observé aucune différence importante entre les valeurs de pH, de PCO_2, de PO_2 et de BE des trois groupes.

Et bien que les écarts du PCO_2 relevé 5, 10, 30, 60 et 120 min. après l'accouchement et comparé aux valeurs d'une minute aient été beaucoup plus grands que pour le groupe de contrôle, on n'a pu retenir un résultat significatif du point-de-vue statistique que pour les valeurs enregistrées 10 min. après l'accouchement.

En conclusion, nous pouvons résumer les données obtenues comme suit:

1. **l'administration de naloxone aux nouveaux-nés après l'accouchement n'a produit aucun trouble chez ces derniers,**
2. **dans les cas de dépression respiratoire foetale et néonatale causée par les analgésiques narcotiques, l'administration de naloxone est susceptible d'accélérer et d'accroître l'élimination de CO_2** et de stimuler la respiration, la dose la plus bénéfique se situant probablement entre 0,01–0,02 mg/kg ou 0,04 au total.

Ceci signifie qu'en cas de dépression respiratoire néonatale dûe à des analgésiques narcotiques, on peut administrer du naloxone sans danger et avec succès.

Mots-clés: Analgésie, antagonistes, déhydrobenzpéridol, dépression respiratoire, gaz sanguins, naissance, naloxone, nouveau-né, péthidine, statut acido-basique.

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